REMARKS

Status of the Claims

Claims 32-34, 36-38, 40, 41, 43, 44 and 46 are pending in the application.

Claims 32-34, 36-38, 40, 41, 43, 44 and 46 have been rejected.

By way of this amendment, claim 37 has been amended and new claims 47-51 have been added.

Upon entry of this amendment, claims 32-34, 36-38, 40, 41, 43, 44 and 46-51 will be pending.

Summary of the Amendment

Claim 32 has been amended to refer to the anti-Vpr monoclonal antibodies being present in an amount effective to reduce the rate of viral production in an HIV infected individual. Support for this amendment is found throughout the specification such as on page 60.

Claim 37 has been amended to indicate that the anti-Vpr antibodies can inactivate Vpr activity of enhancing the rate of HIV viral production. In addition, claim 37 has been amended to clearly refer to the anti-Vpr antibodies being present in an amount effective to reduce the rate of viral production in an HIV infected individual. Support for this amendment is found throughout the specification such as on page 60 and page 65.

New claim 47 refers to specific embodiments of the compositions of the invention. Support for this amendment is found throughout the specification such as on page 65.

New claims 48-51 refer to specific embodiments of the methods of the invention. Support for this amendment is found throughout the specification such as on page 60.

Rejection under 35 U.S.C. §103(a)

Claims 32, 36, 37, 38, and 40 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Sato et. al. (1999) in view of Matsushita (1998). Specifically, the Office alleges that it would have been *prima facie* obvious to one having ordinary skill in the art at the

time the invention was made to prepare pharmaceutical compositions taught by Matsushita comprising anti-Vpr antibodies taught by Sato et al. Applicants respectfully disagree.

Sato et al. discloses anti-Vpr polyclonal antibody compositions used to identify Vpr expression in a Western blot.

Matsushita discloses compositions comprising anti-gp120 monoclonal antibodies.

It is asserted that it would have been prima facie obvious to one skilled in the art to combine the teachings of Sato et al and Matsushita to provide the claimed invention. It is asserted that those skilled in the art would have been motivated to prepare monoclonal antibodies as taught by Matsushita against immunogenic targets taught by Sato et al. to produce a high affinity immunological reagent useful in diagnostic and other applications. Moreover, it is asserted that those skilled in the art would have been motivated to prepare sterile compositions to improve shelf life and stability.

Matsushita refers to other monoclonal antibodies against other HIV proteins but indicates that none of the other antibodies bind to gp120 which is important in "preventing and treating AIDS" (col 2., lines 26-28). Matsushita states that attempts have been previously made to find monoclonal antibodies which neutralize AIDS viruses and which may be used ot treat and diagnose AIDS (col 2., lines 33-36). Matsushita discloses compositions comprising anti-gp120 monoclonal antibodies because Matsushita states that his monoclonal antibody is capable of "significantly neutralizing (hereinafter defined) HIV by binding with an epitope of the HIV envelope antigens." (col. 2, lines 50-53). The Matsushita reference further defines "neutralizing" as:

> the inhibition of HIV infection by cell-free virons and/or the inhibition of cell-to-cell infection such as the formation of syncytia by the fusion of HIV-infected cells with uninfected cells induced by the interaction of gp120 with CD4 molecules.

(col 2. lines 58-62). Accordingly, Matsushita teaches the preparation of monoclonal antibodies which can inhibit HIV infections. Matsushita teaches the preparation of monoclonal antibodies against HIV proteins involved in viral infection

Nowhere does Matsushita describe, mention, or suggest using an antibody to inactivate the biological activity of a viral protein involved in enhancing the rate of viral production in already infected cells. Matsushita teaches inhibiting infection, not inhibiting replication. Nowhere does Matsushita describe, mention, or suggest antibody compositions present in an amount effective to reduce the rate of viral production in an HIV infected individual. Nowhere does Matsushita describe, mention, or suggest antibodies compositions comprising antibodies that inactivate an HIV protein activity to reduce the rate of HIV viral production present in an amount effective to reduce the rate of viral production in an HIV infected individual.

Nowhere does Sato et al describe, mention, or suggest that Vpr has a biological activity involved in enhancing the rate of viral production in already infected cells. Nowhere does Sato et al describe, mention, or suggest using their antibody to inactivate any biological activity. Sato et al. teaches detecting Vpr expression, not inhibiting activity. Nowhere does Sato et al. describe, mention, or suggest antibody compositions present in an amount effective to reduce the rate of viral production in an HIV infected individual. Nowhere does Sato et al. describe, mention, or suggest antibodies compositions comprising antibodies that inactivate an HIV protein activity to reduce the rate of HIV viral production present in an amount effective to reduce the rate of viral production in an HIV infected individual.

One skilled in the art would not combine Matsushita with Sato et al. because Matsushita teaches away from the claimed invention. Matsushita teaches targeting viral proteins involved in infection in contrast to other protein targets as a viable strategy to combat HIV. One skilled in the art would not consider the teachings of Matsushita in connection with Vpr and antibody compositions comprising anti-Vpr antibodies. One skilled in the art would conclude based upon the teachings of Matsushita that anti-Vpr antibodies could not be useful in anti-HIV compositions and would therefore not use the teachings of Matsushita in combination with those of Sato et al. A prima facie case for obviousness cannot be establish if one of the references teaches away from the invention. Matsushita teaches away from the invention. Accordingly the combination does not establish a prima facie case.

Even if one skilled in the art were to combine the teachings of Matsushita with those of Sato et al., they would not yield the present invention. With regards to claims 37, 38 and 40, the combination of Matsushita and Sato et al. does not yield a pharmaceutical composition comprising anti-Vpr monoclonal antibodies that reduce Vpr's effect on the rate of viral production in already infected cells and that are present in an amount effective to reduce the rate of viral production in an HIV infected individual. Neither reference teaches or suggests Vpr's role in viral replication, much less that sufficient antibodies could be included in a composition and accordingly the combination does not establish a prima facie case.

The claimed invention is not obvious over Sato in view of Matsushita. Applicants respectfully request that the rejection of claims 32, 36, 37, 38 and 40 under 35 U.S.C. § 103(a) as unpatentable over Sato in view of Matsushita be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 33, 34, 41, 43, 44, and 46 stand rejected under 35 U.S.C. § 112, first paragraph, because it is alleged that the specification does not enable one of ordinary skill to which it pertains, or with which it is mostly nearly connected, to make and/or use the invention (Office Action, p. 3). The Office asserts that the specification does not enable one of ordinary skill in the art to use the invention because: (1) the disclosure fails to provide adequate guidance pertaining to the structural and functional characteristics of the anti-Vpr antibodies present in the pharmaceutical composition (Office Action, p.4); (2) the disclosure fails to provide adequate guidance pertaining the role of extracellular versus intracellular Vpr in HIV pathogenesis and disease progression (Office Action, p.5); (3) the claims are broadly directed to any population of anti-Vpr antibodies (Office Action, p.5); and (4) the state-of-the-art can be characterized by unpredictability and frequent failure (Office Action, p.6). Applicants traverse the rejection and respectfully request reconsideration because the claimed invention is enabled.

Applicants note that it is well established that the description is presumed to be enabled and that, in order to sustain an enablement rejection under the first paragraph of 35 U.S.C. § 112, the Examiner must establish, using reasoning and evidence, that those skilled in the art would

doub in the objective truth of Applicant's assertion that the claimed invention is enabled. See, e.g. *re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also M.P.E.P. § 2163

Item (1) of the analysis provided in the rejection states that claims are not enabled beca se the disclosure fails to provide adequate guidance pertaining to the structural and func onal characteristics of the anti-Vpr antibodies present in the claimed composition. The Exar iner points out that the specification is silent with respect to the epitope recognized by the antib odies, the affinity and avidity of the antibodies, and pharmacological properties of the antib odies. Gait and Karn (1995) are cited, presumably as evidence that pharmacological prop rties represent obstacles which must be overcome. Applicants respectfully urge that the abse ce of specific disclosure with respect to epitope recognized by the antibodies, the affinity and a vidity of the antibodies, and pharmacological properties of the antibodies does not render the i vention not enabled. nothing in the record supports the conclusion that epitopes recognized by th e antibodies, and the affinity and avidity of the antibodies must be disclosed to enable one skill d in the art to practice the invention. Likewise, Gait and Karn (1995) describe problems that o ccur in drug development, specifically small molecule antiviral enzyme inhibitors, not antib odies, but they do not indicate that absent a pharmacological profile, the enablement requ rement for is not established. Rather, their discussion is directed at development of drugs whic h must be proven safe and effacious by regulatory agencies. The standards used in such eval ations are different from those used to determine if an invention is enabled. Gait and Karn (199) state that even when pharmacokinetic problems are solved, new problems emerge such as sequ stration by serum proteins, drug resistance and uneven distribution. Thus, for example, Gait nd Karn (1995) point out that drug resistance makes usefulness limited because the drug even ually stops working. These problems may limit a drugs clinical usefulness and commercial valu but the drug is enabled.

Examiner further concludes in item (1) that, because Vpr is a regulatory protein, Vpr may not b e readily accessible to circulating antibodies. No reasoning or evidence is provided to supp rt this assertion. Regulatory functions of proteins do not correlate to the protein's

acce sibility to antibodies. Even if there were a relationship between a protein's regulatory func ion and accessibility to antibodies, Examiner shows no evidence to support his position. The pecification reports that the antibodies inactivate the biological effect of Vpr to reduce the rate f viral production. No evidence or reasoning have been made to contradict this conclusion.

Item (2) of the analysis provided in the rejection states that the disclosure fails to provide adec ıate guidance pertaining to the role of extracellular versus intracellular Vpr in HIV path genesis and disease progression. It is asserted that one of ordinary skill in the art could not pred ct whether extracellular Vpr plays a significant role in pathogenesis of HIV. No evidence or re ısoning is provided by the Examiner in support this conclusory statement.

On the other hand, in the declaration of Dr. David Weiner submitted pursuant to 37 C.F.R. § 1.132, Dr. David Weiner refers to his manuscript published in the Journal of Virology, Febr ıary 1995, 69(2):1243-52 (hereinafter "the Levy reference") which includes evidence of the corr lation between extracellular Vpr and disease. The Levy reference clearly describes the dran atic effect that low concentrations of extracellular Vpr protein have on HIV-infected cells (p. 1245 – 1260, Figs. 2 through 10 and accompanying discussion). The Levy reference also clea ly addresses the clinical relevance of such a result by its discussion of cellular pern issiveness within HIV-infected humans:

> Virus disintegration or immune lysis of virions could release Vpr into bodily fluids where autocrine or paracrine regulation of HIV replication would ensue. We have recently found biologically active Vpr in the serum and cerebral spinal fluid of HIV-infected individuals in levels that correlate with the degree of p24 antigenemia observed and disease state. The high level of virus replication that occurs after initial infection, and also at the last stage of disease, may be accelerated by a positive feedback mechanism driven by free extracellular Vpr. Vpr could also provide a means to reactivate virus expression in latently infected cells in vivo.

(p. 1250, col. 2, paragraph 2, lines 6-17) (citations omitted).

It is further asserted based upon item (2), that because large amounts of virus are proc ıced per day, one of ordinary skill in the art would not be able predict whether the

phar. naceutical composition could be efficiently titered and targeted to the appropriate com] artments within a patient. Methods of titering and efficient targeting of pharmaceutical com· ositions are readily known to those of ordinary skill in the art. These are routine within the field Moreover, the claimed invention relates to reducing the rate viral production by neut alizing the biological effect of a viral protein. Mere evidence of high levels of viremia do not r fute evidence provided in the specification which demonstrate that anti-Vpr antibodies redu e the rate of viral production. Nothing in the record supports a conclusion that the skilled artis n would expect that the specification fails to provide adequate guidance to reduce viral prod.ction in spite of the large numbers of viruses that are produced in a given patient per day.

Item (3) refers to the claim breadth as being excessive and states that the specification is silen with respect to properties of an antibody compositions. Inherent in this assertion is that the clair s are not enabled because the properties of an antibody compositions are not recited. No evid nce or reasoning is provided by the Examiner in support of such a conclusion.

The evidence provided in support of the rejection based upon item (4), that the state-of-the-a t can be characterized by unpredictability and frequent failure, includes the following refer nces, all of which discuss technology that is different and distinct from that which cons itutes the claimed invention: Lindhardt, et. al. (1989), Jacobson, et. al. (1993), Karwowska, et. a . (1991), and Kohler, et. al. (1992). For instance, Lindhardt discusses natural immunity gene ated against p24 and the immunity's inability to prevent viral infection. The present appl.cation does not describe natural immunity involved in preventing viral infection. Therefore, Lind ıardt has no bearing on the predictability of compositions design to block the biological func ion of Vpr. Kohler, Karwowska, and Jacobson all describe difficulties either (a) developing vacc nes that induce immunity to kill infected cells or neutralize viral particles; or, (b) diffi ulties with passive immunity protocols which include antibodies administered to patients that lock HIV infection. The claimed invention is not related to conferring immunity against infe tion nor is it related to blocking HIV infection through administration of antibodies. The clair ed invention is related to inactivating the biological effect of a viral protein to reduce the rate of viral production.

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When the totality of evidence is viewed as a whole, little or no and reasoning has been provided to raise doubt that the claimed invention is enabled. In the absence of such evidence and reasoning, the law requires that the applicants assertion that the invention as enabled be accepted. Nonetheless, in the instant application, the evidence of record clearly supports such a finding. Thus, even though the burden is not properly shifted to the Applicant and no further evidence is required, the evidence of record, taken as a whole, fully supports a conclusion that those skilled in the art would conclude that the claims are enabled and that one skilled in the art, armed with the Applicant's disclosure and ordinary skill could practice the claimed invention.

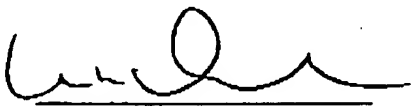
The specification enables the claimed invention. The application is in compliance with the requirements of the first paragraph of section 112. Applicants respectfully request that the rejection of claims 33, 34, 41, 43, 44, and 46 under 35 U.S.C. §112, first paragraph, be withdrawn.

Conclusion

Claims 32-34, 36-38, 40, 41, 43, 44 and 46-51 are in condition for allowance. A notice of allowance is earnestly solicited. Applicants invite the Examiner to contact the undersigned at 215.665.5592 to clarify any unresolved issues raised by this response.

As indicated on the transmittal accompanying this response, the Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-1275.

Respectfully submitted,



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Date: Dec 28 2006

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